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Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes

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ABSTRACT

Background: Most patients with myelodysplastic syndromes (MDS) require transfusions at the risk of iron overload and associated organ damage, and death. Emerging evidence indicates that iron chelation therapy (ICT) could reduce mortality and improve survival in transfusion-dependent MDS patients, especially those classified as International Prognostic Scoring System (IPSS) Low or Intermediate-1 (Low/Int-1).
Methods: Follow-up of a retrospective study. Sample included 127 Low/Int-1 MDS patients from 28 centers in Belgium. Statistical analysis stratified by duration (≥6 versus <6 months) and quality of chelation (adequate versus weak).

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Transfusion
Transfusion dependency
Iron overload
Chelation therapy
Cardiac death

Results: Crude chelation rate was 63% but 88% among patients with serum ferritin ≥1000 μg/L. Of the 80 chelated patients, 70% were chelated adequately mainly with deferasirox (26%) or deferasirox following deferoxamine (39%). Mortality was 70% among non-chelated, 40% among chelated, 32% among patients chelated ≥6 m, and 30% among patients chelated adequately; with a trend toward reduced cardiac mortality in chelated patients. Overall, median overall survival (OS) was 10.2 years for chelated and 3.1 years for non-chelated patients ($p < 0.001$). For patients chelated ≥6 m or patients classified as adequately chelated, median OS was 10.5 years. Mortality increased as a function of average monthly transfusion intensity (HR = 1.08, $p = 0.04$) but was lower in patients receiving adequate chelation or chelation ≥6 m (HR = 0.24, $p < 0.001$).
Conclusion: Six or more months of adequate ICT is associated with markedly better overall survival. This suggests a possible survival benefit of ICT in transfusion-dependent patients with lower-risk MDS.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders impairing the production of normal mature blood cells and characterized by cytopenias, cytologic dysplasia, and risk of transformation to acute myeloid leukemia (AML) [1–6]. From 60% to well over 90% of MDS patients develop anemia [3,7–10], with up to 60% of these patients presenting with severe anemia (hemoglobin level < 10 g/dL). The majority of patients will require red blood cell (RBC) transfusions [3] to manage the anemia, prevent anemia-related comorbidity, maintain physical performance, and improve quality of life [11]. In 40% of patients transfusion is the sole therapeutic option.

Transfusion dependence is associated with increased risks of disease progression [1,3,6,7] and death [1,6,7,12]. After about ten to twenty transfusions [5,13,14], transfusion-dependent MDS patients invariably develop iron overload at a rate of approximately 0.5 mg/kg/day [15]. For every 500 μg/L increase in serum ferritin above 1000 μg/L, mortality risk rises by 30% [6]. Observational studies have shown that iron chelation therapy (ICT) lowers iron burden [16–20] and is associated with better survival [21–23]. In one study, median survival time for patients with International Prognostic Scoring System (IPSS) Low or Intermediate-1 (Low/Int-1) risk chelated for at least 6 months was 124 months since first transfusion compared to 53 months for those not chelated [21]. A study including also higher risk MDS patients reported median survival times of 74 and 49 months, respectively [22]. In a third study, 80% of patients receiving ICT were still alive after 4 years compared to 44% of patients not receiving ICT [23]. ICT is recommended in transfusion-dependent patients and should be initiated prophylactically before clinically significant iron accumulation occurs [13]. Patients with lower-risk MDS and high transfusion requirements may be more likely to benefit from ICT [1,24,25]. The recently published European LeukemiaNet guidelines recommended ICT should be considered in transfusion-dependent patients with refractory anemia, refractory anemia with ring sideroblasts, or MDS with isolated 5q deletion and a serum ferritin level higher than 1000 ng/mL after approximately 25 units of red cells [26].

We recently reported on a retrospective study (CICL670ABE02, hereafter ABE02) evaluating iron status and its management in 193 transfusion-dependent MDS patients from 29 centers in Belgium [27]. A follow-on study (CICL670ABE03, hereafter ABE03) aimed to investigate the effect of ICT versus no such treatment on overall survival. While we analyzed the data for all patients, we report here on the subsample of MDS patients classified as Low/Int-1 at diagnosis as these patients may benefit most from ICT [1,24,25].

2. Methods

2.1. Design and procedures

As a follow-on investigation to the prior ABE02 study, the present ABE03 study was a multicenter, retrospective, observational, non-interventional study [27]. Retrospective chart reviews for the ABE02 study were performed between September and November 2008 and yielded 193 patient records from 29 centers. As available from medical records, data were recorded for each patient from the time of diagnosis of MDS. This period ranged from 0 to 32 years with a median time since diagnosis of 2 years and a mean ± SD of 3.4 ± 4.0 years.

In 2010, 28 of these centers representing 186 patients agreed to participate in the ABE03 follow-on study (net loss of 7 patients). Chart reviews were conducted between October 2010 and March 2011 and covered the two-year period since the end of the ABE02 study. For patients who died or were lost to follow-up during the observational study period, the chart review was conducted up to their last recorded time point.

The primary endpoint was overall survival (OS), defined as time between MDS diagnosis and death (from any cause), lost to follow up (censored), or end of study.

The study was approved by the Ethical Committee of each participating center. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association as subsequently amended.

2.2. Iron chelation therapy

Patients were considered to have received chelation therapy if they were treated with either deferoxamine or deferasirox. No patients received deferiprone. We differentiated between patients chelated for at least six months and those chelated for a shorter period. Further, in order to allow comparison between chelation therapies, and in analogy with previous publications [21], patients receiving ICT were classified as either "adequately chelated" or "weakly chelated". The definitions for these terms were adopted from Rose et al. [21] to discriminate between patients receiving the iron chelator in an optimal (or "adequate") versus suboptimal ("or "weak") way, and this independent of the administration route or the novelty of the drug. Hence, slow subcutaneous deferoxamine infusions administered on multiple days/week or deferasirox at any dose was considered "adequate chelation". Alternately, deferoxamine by any other method of administration (intravenously once after or during each transfusion or subcutaneously as a bolus infusion or other) was considered "weak chelation".

2.3. Variables

Data as available from the medical record and used in the statistical analysis included: patient demographics (age and gender); current medical status and comorbidities (diabetes, signs of heart failure, other cardiovascular disease, abnormal liver tests, and other severe comorbidities with potential impact on survival) at entry into study ABE02; history of MDS (date of diagnosis, French-British-American [FAB] and/or World Health Organization [WHO] classification at diagnosis, and IPSS prognostic classification at diagnosis); cytogenetic risk group at diagnosis (conventional karyotype or fluorescence in situ hybridization); previous MDS treatments (growth factors, immunomodulatory agents, chemotherapy, and allogeneic transplantation); most recent red blood cell hematology (hemoglobin [Hb], transferrin saturation [TSAT] and serum ferritin levels); blood transfusion history (number of red blood cell [RBC] units since diagnosis, number of RBC units in past 4 months); progression to either acute myeloid leukemia (AML) or more severe MDS; and iron chelation therapy (if any, agent, and route of administration). Average transfusion intensity was calculated as the ratio between total number of RBC transfusions received and the difference in months between first RBC transfusion and last date recorded.

2.4. Statistical analysis

Descriptive statistics for continuous variables included measures of central tendency and dispersion; for discrete variables, counts, percentages, and proportions were calculated. Tests of significance included Student's *t*-test for independent samples and analysis of variance for respectively 2 and ≥3 subgroup comparisons on continuous variables; and χ^2-based contingency analysis with, as applicable, Fisher's exact test for discrete variables. Bonferroni-class corrections were used to correct for multiplicity.

Actuarial probability of OS was approximated using the Kaplan–Meier product limit method, and comparisons between/among Kaplan–Meier curves were performed using the log-rank test. For those patients alive at the end of the study, data were censored at the time of their last recorded visit. Multivariate Cox Proportional-Hazard (PH) analysis was used to identify independent predictors of OS, while adjusting for the potential confounding effect of age. Covariates satisfying the proportional hazards assumption were included in this analysis. Statistical significance was set at $\alpha = 0.05$ two-tailed. Statistical analysis was performed using SPSS® v.20 [28].

3. Results

3.1. Data availability

Of the 186 patients, 127 (88%) were classified as Low/Int-1 at diagnosis. These patients constituted the analysis set. The mean time difference between patients' last data point in ABE02 and the follow-up data point in ABE03 was 25.4 ± 1.3 months. Of the 127 patients, 55 (43%) were still alive at the time of data recording for the ABE03 study, 65 (51%) had died, and 7 (6%) were lost to follow-up.

3.2. Characteristics of the Low/Int-1 patients

Table 1 summarizes patient characteristics and clinical status at entry into ABE02 for all 127 Low/Int-1 patients, and comparing patients who were (*n* = 80, 63%) and who were not chelated (*n* = 47, 37%); and, among the 80 chelated patients, those chelated for at least 6 months (*n* = 62, 49%). The mean (±SD) age at the time of MDS diagnosis was 72 (±9.2) years (range 40–95) with patients chelated for 6 months or more being slightly younger than non-chelated patients ($p = 0.04$). The difference in gender proportions was not statistically significant.

Some centers used the FAB, some the WHO, and some both classification methods. Per data availability, the most common types of MDS were refractory anemia without or with ringed sideroblasts (57% per WHO and 90% per FAB). Similarly, 71 (85%) of the 84 patients with reported cytogenetic results fell in the favorable risk category. There were no statistically significant differences by chelation status for WHO, FAB, and karyotype classification. Most patients (77%) had at least one comorbidity of interest with cardiovascular disease (including signs of heart failure) being the most common (76%), with no significant differences by chelation status.

About one-fifth (27 or 21%) of patients had never received a specific treatment for their MDS. The proportion of untreated patients did not differ significantly between chelated (28%) compared to non-chelated (17%) patients (p = not significant [ns]). Erythropoietic growth factors were the most common treatment (55%) with no statistically significant differences by chelation status (all p = ns); neither were there any statistically significant differences in the proportions of other MDS treatments by chelation status (all p = ns), or receiving no MDS treatment at all (all p = ns).

3.3. Anemia, transfusion, and iron status

Mean ± SD Hb concentrations were 9.1 ± 1.9 g/dL (range 3.2–13.9) at enrollment into ABE02 and 8.7 ± 1.9 g/dL (range 4.8–15.9) at the end of ABE03 (Table 1). The differences between non-chelated and, respectively, chelated ($p = 0.004$) and chelated ≥ 6 months ($p = 0.01$) patients' mean last recorded Hb level were statistically significant. On average, patients had received 13.3 ± 9.5 RBC transfusions in the past 4 months, with non-chelated patients on average having been given fewer transfusions than chelated patients ($p = 0.02$) or patients chelated ≥ 6 months (≥6 m; $p = 0.04$). The distribution of transfusions (0–10, 11–20, and 21–50) trended toward proportionately fewer transfusions among non-chelated versus chelated and chelated ≥6 m (both $p = 0.01$). Hence the mean number of units of RBCs transfused was lower for non-chelated compared to chelated patients ($p = 0.001$) and especially patients chelated ≥6 m ($p < 0.001$). Average transfusion intensity per month was 2.8 ± 2.9, with no significant differences between non-chelated, chelated, and chelated ≥6 m patients (all p = ns). The most recent serum ferritin levels averaged 2925 ± 2998 and the highest recorded level averaged 3984 ± 4292 with no statistically significant differences by chelation status (all p = ns).

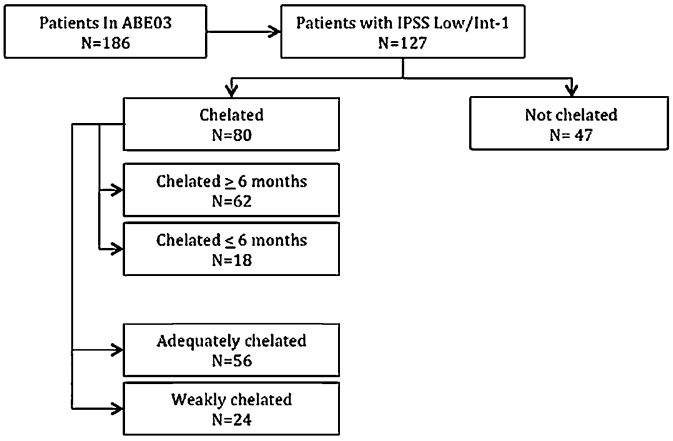

Fig. 1. Classification chart of patients by chelation status, with subclassification by duration and quality of iron chelation therapy.

3.4. Iron chelation therapy

The crude chelation rate was 63%, but 88% among patients with serum ferritin concentrations ≥1000 μg/L. Thirty-five percent received deferoxamine; 26.3% were treated with deferasirox; and for 39% deferasirox following prior deferoxamine therapy.

Fig. 1 presents a classification chart of patients with Low/Int-1 MDS by chelation status; and within the chelated category, by duration and quality of chelation. Of the 80 chelated patients, 56 (70%) were chelated adequately while 24 (30%) were chelated weakly (see also Table 2). In terms of duration, 62 (78%) were treated for ≥6 m, of which 50 (81%) received adequate chelation.

3.5. Survival outcomes

In total, 65 patients (52%) had died since the end of the ABE02 study, but proportionately more so among the non-chelated (70%) patients compared to the chelated patients (40%; $p = 0.002$) and those chelated ≥6 m (32%) ($p = 0.001$) (Table 2). In addition, there were significantly fewer patient deaths among adequately chelated patients (30%) relative to those chelated weakly (63%) ($p = 0.01$). There was a trend toward reduced cardiac deaths in chelated versus non-chelated patients ($p = 0.05$). The mortality rate from progression of MDS disease did not differ by chelation status (all p = ns).

Other primary causes of death are listed here in descending order of frequency among the 127 patients (note that some patients had more than one identified cause of death hence totals may exceed the total number of deceased patients in Table 2): infection/septicemia (*n* = 7), respiratory (*n* = 6), vascular (*n* = 4), progressive deterioration (incl. old age) (*n* = 4), unknown cause (incl.

Table 1
Characteristics and clinical status of patients classified as IPSS Low or Intermediate-1 by chelation status.

	All patients (*N* = 127)	Non-chelated (*N* = 47)	Chelated (*N* = 80)	Chelated ≥ 6 months (*N* = 62)	*P*[*]	*P*[**]
Age in years at MDS diagnosis, *mean (SD)*	72 (9.2)	73 (9.0)	71 (9.3)	70 (9.4)	0.11	0.04
Gender, *n (%)*						
Male	56 (44)	20 (42)	36 (45)	30 (48)	0.85	0.57
Female	71 (56)	27 (57)	44 (55)	32 (52)		
Most recent hemoglobin level, *mean (SD)*	8.7 (1.9)	9.4 (2.2)	8.4 (1.6)	8.4 (1.7)	0.008	0.02
Missing, *n*	1	1	0	0		
RBC transfusions in past 4 months, *mean (SD)*	13.3 (9.5)	10.7 (8.4)	14.9 (9.8)	14.2 (8.7)	0.02	0.04
0–10 transfusions, *n (%)*	45 (39)	24 (56)	21 (28)	15 (27)		
11–20 transfusions, *n (%)*	52 (44)	13 (30)	39 (53)	34 (61)	0.01	0.01
21–50 transfusions, *n (%)*	20 (17)	6 (14)	14 (19)	7 (13)		
Missing, *n*	10	4	6	6		
Total number of RBC units transfused, *mean (SD)*	105 (92)	70 (90)	127 (87)	144 (91)	0.001	<0.001
Missing, *n*	4	0	4	4		
Average transfusion intensity per month,[a] *mean (SD)*	2.8 (2.9)	2.6 (3.5)	2.9 (2.5)	2.7 (1.2)	0.58	0.85
Missing, *n*	5	0	5	5		
Most recent serum ferritin level, *mean (SD)*	2925 (2998)	3025 (2755)	2868 (3144)	3027 (3455)	0.77	1.00
Missing, *n*	3	2	1	1		
Highest recorded serum ferritin level, *mean (SD)*	3984 (4292)	4220 (5091)	3862 (3849)	3865 (3997)	0.69	0.71
<1000 μg/L, *n (%)*	19 (16)	9 (22)	10 (13)	8 (13)		
1000–1999 μg/L, *n (%)*	20 (17)	4 (10)	16 (20)	14 (23)		
2000–2999 μg/L, *n (%)*	29 (24)	12 (29)	17 (21)	11 (18)	0.27	0.15
3000–3999 μg/L, *n (%)*	15 (12)	6 (15)	9 (11)	6 (10)		
≥4000 μg/L, *n (%)*	38 (31)	10 (24)	28 (35)	23 (37)		
Missing, *n*	6	6	0	0		
IPSS classification at diagnosis, *n*[b]						
Low	54	18	36	28	0.58	0.56
Intermediate-1	73	29	44	34		
WHO classification at diagnosis, *n*[b]						
RA	27	10	17	14	0.11	0.12
RARS	24	5	19	17		
RCMD	14	7	7	5		
RSCMD	1	1	0	0		
RAEB-I	5	1	4	3		
RAEB-II	1	0	1	1		
5q-syndrome	15	9	6	5		
Unclassified	3	0	3	2		
FAB classification at diagnosis, *n*[b]						
RA	60	25	35	26	0.48	0.19
RARS	34	8	26	22		
RAEB	7	2	5	2		
RAEB-T	1	0	1	1		
CMML	2	1	1	0		
Karyotype, *n*[b]						
Favorable (normal, isolated 5q-, isolated 20q-, or deletion Y)	71	25	46	36	0.09	0.11
Poor (any chromosome seven anomaly or ≥3 aberrations)	7	4	3	2		
Intermediate (all other anomalies)	6	0	6	4		
MDS treatments ever received, *n*[c]						
Erythropoietic growth factors	70	22	48	38	0.20	0.17
Immunomodulatory agents	32	13	19	17	0.68	1.00
ATG ± cyclosporin	3	0	3	3	0.30	0.26
Low dose chemotherapy	19	5	14	11	0.44	0.41
Intensive chemotherapy	3	1	2	2	1.00	1.00
Allogeneic transplantation	4	2	2	2	0.63	1.00
Hypomethylating agents	7	5	2	2	0.10	0.24
Other growth factors	14	4	10	8	0.57	0.55
Other treatments	14	3	11	11	0.25	0.09
No treatment	27	13	14	10	0.19	0.16

[a] Average transfusion intensity was calculated as the ratio between total number of RBC transfusions received and the difference in months between the first RBC transfusion and the last study date recorded.
[b] On available data and as reported by investigators.
[c] Patients may receive more than one treatment.
AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; FAB = French-American-British; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndrome; RA = refractory anemia; RAEB-I = refractory anemia with excess of blasts-I; RAEB-II = refractory anemia with excess of blasts-II; RAEB-T = refractory anemia with excess of blasts in transformation; RARS = refractory anemia with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RSCMD = refractory sideroblastic cytopenia with multilineage dysplasia; SD = standard deviation; WHO = World Health Organization.
[*] *p*-Value for differences between chelated and non-chelated patients.
[**] *p*-Value for differences between chelated at least 6 months and non-chelated patients.

Table 2
Iron chelation therapy and outcomes.

Iron chelation therapy, *n (%)*	
Non-chelated	47 (37)
Chelated	80 (63)
Weakly chelated	24 (30)
Adequately chelated	56 (70)
Deferoxamine	28 (35)
Deferasirox	21 (26)
Deferoxamine and deferasirox	31 (39)

Outcomes, *n (%)*
All Patients, n (%)

	All (*N* = 127)	Non-chelated (*N* = 47)	Chelated (*N* = 80)	*P*
Death	65 (51)	33 (70)	32 (40)	0.002
Cause of death				
Cardiac	8 (6)	6 (13)	2 (3)	0.05
MDS progression	22 (17)	7 (15)	15 (19)	0.64
Other causes of death	40 (32)	21 (45)	19 (24)	0.02

Patients who were either not chelated or chelated at least 6 months, n (%)

	All (*N* = 109)	Non-chelated (*N* = 47)	Chelated >6 months (*N* = 62)	*P*
Death	53 (49)	33 (70)	20 (32)	<0.001
Cause of death				
Cardiac	8 (7)	6 (13)	2 (3)	0.07
MDS progression	16 (15)	7 (15)	9 (14)	1.00

patients who died outside of the hospital) ($n = 3$), and two each for trauma or gastro-intestinal causes, death related to chemotherapy, or death due to other malignancies.

The Kaplan–Meier curves and associated statistical results for OS by various chelation stratifications (chelated versus non-chelated; adequately versus weakly versus non-chelated; and non-chelated versus chelated ≥6 m) are presented in Figs. 2–4. Median OS was 10.2 years for chelated and 3.1 years for non-chelated patients ($p < 0.001$). For patients chelated ≥6 m or patients classified as adequately chelated, median OS was 10.5 years. Median OS was higher among patients chelated ≥6 m versus non-chelated patients ($p < 0.001$); among patients chelated ≥6 m versus patients not chelated ($p < 0.001$); among patients adequately versus weakly chelated ($p = 0.001$); and among patients adequately chelated versus those not chelated ($p < 0.001$). Median survival did not differ significantly between weakly and non-chelated patients (p = ns).

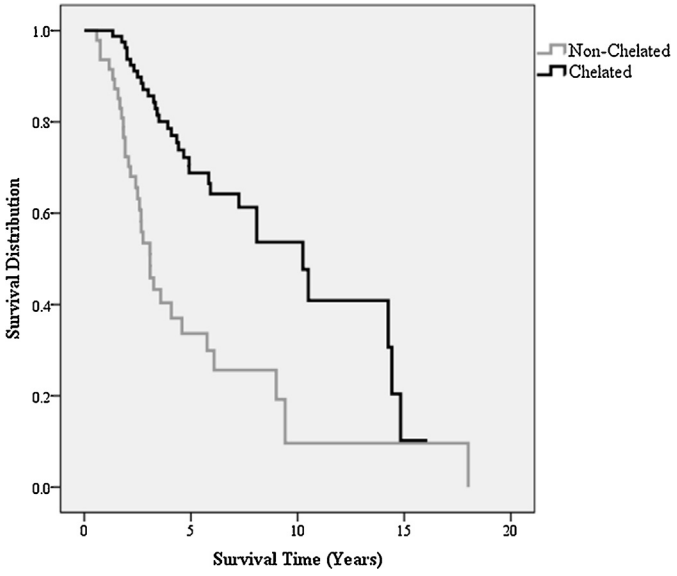

Fig. 2. Overall survival (OS) among non-chelated ($n = 47$) versus chelated patients ($n = 80$). Median (SE) OS was 3.1 (0.4) months among non-chelated and 10.2 (1.4) years among chelated patients ($p < 0.001$).

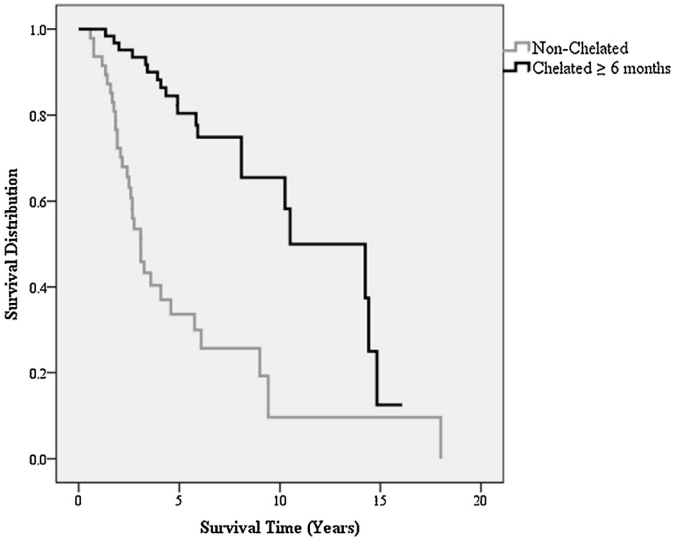

Fig. 3. Overall survival (OS) among non-chelated ($n = 47$), weakly chelated ($n = 24$), and adequately chelated ($n = 56$) patients. Median (SE) OS was 3.1 (0.4) years among non-chelated, 4.3 (0.8) years among weakly chelated, and 10.5 (2.0) years among adequately chelated patients.

Preliminary unadjusted univariate analyses identified four parameters with a statistically significant association with survival: RBC units received in the preceding four months ($p = 0.049$); average monthly transfusion intensity ($p = 0.023$); adequate chelation ($p = 0.002$); and chelated ≥6 m ($p < 0.001$). Because of the

Table 3
Cox Proportional-Hazards model for overall survival.

Parameters	Hazard ratio	95% CI	*P*
Male gender[a]	1.91	1.10–3.31	0.02
Adequate chelation[b]	0.22	0.12–0.41	<0.001

[a] Reference is female gender.
[b] Reference category is no chelation.

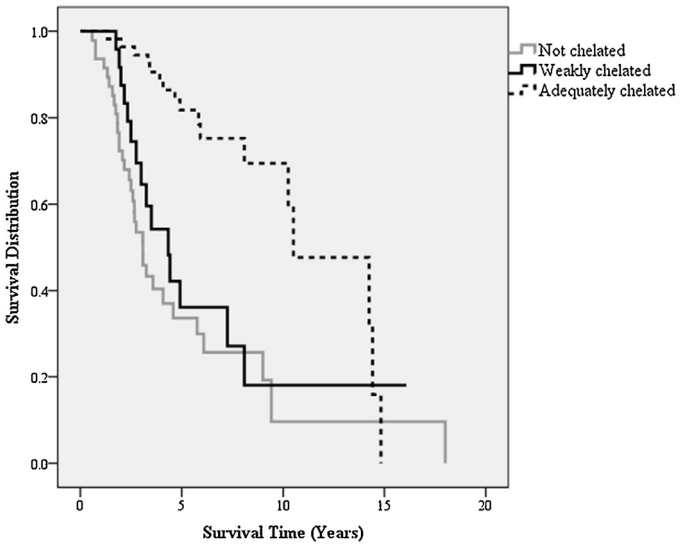

Fig. 4. Overall survival (OS) among non-chelated ($n = 47$) versus patients chelated > 6 months ($n = 62$). Median (SE) OS was 3.1 (0.4) years among non-chelated and 10.5 (2.2) years among patients chelated > 6 months ($p < 0.001$).

convergence of adequate chelation and chelation of ≥6 m in most patients, the former variable was retained. In the multivariate analysis (Table 3), while controlling for age (and thus age-related mortality), male gender was associated with higher mortality risk (HR = 1.91, $p = 0.02$) whereas adequate chelation had a strong mitigating effect on mortality (HR = 0.22, $p < 0.001$). Similar results were obtained when chelation ≥6 m was substituted by being adequately chelated (data not shown).

4. Discussion

In this sample of 127 transfusion-dependent patients with lower-risk MDS we demonstrate that iron chelation therapy, especially with an adequate regimen and for 6 months or more, is associated with prolonged survival. Patients who received appropriate iron chelation tended to live in excess of ten years following their diagnosis of MDS, compared to about 3 years for non-chelated patients. The mortality rate was 70% among non-chelated patients as opposed to 32% among those chelated for at least 6 months. Modeling revealed that the survival effect of adequate chelation was pronounced but also that male patients tended to be at higher risk for shorter OS. Importantly, there was a trend for reduced cardiac mortality in chelated patients.

Our findings build upon and extend those reported by Rose et al. in French [21] and more recently by Lyons et al. [29] in US centers. In the French study [21] of Low/Int1 patients, 55% of patients received chelation therapy, all for at least 6 months; whereas in the US study of lower risk MDS patients [29] 48% where chelated (including 32% for 6 months or more). These crude rates were lower than the 60% rate observed in our sample. However, all three studies are consistent in their observation that patients treated with ICT have a longer survival time. At 10.2 years in our cohort and 10.3 years in the Rose study, median overall survival times for chelated patients were nearly identical, yet higher than the 8.3 years reported by Lyons et al. [29]. This trend was also evidenced among patients chelated for at least six months: 10.5 years in our study, 10.3 years in the Rose et al. [21] study, and 8.7 years in the Lyons et al. study [29]. These survival times are longer compared to the 6.3 years from a matched-pair analysis from 94 chelated patients reported by Neukirchen et al. [22]. Although the patient cohorts are different, all four studies show better overall survival in chelated patients, indicating that adequate ICT may be beneficial in the Low/Int-1 MDS population.

Our data are in agreement with consensus-based guidelines [23–26,30,31], identifying transfusion-dependent Low/Int-1 risk MDS patients as an important target population for ICT. An additional observation was made regarding the dosing and duration of ICT. Only patients receiving adequate dosing of ICT and treated for at least 6 months had a significant overall survival benefit. Furthermore, despite the higher transfusion need in the chelated patients serum ferritin levels at the end of the observation period were similar in the chelated and the non-chelated patients supporting the efficiency of ICT in reversing transfusional iron overload. However, one should also take into account the contribution to iron overload of increased iron absorption due to ineffective erythropoiesis, particularly among anemic patients.

One limitation of our study is a potential bias in patient selection. For instance, physicians may decide to provide ICT only to patients with a reasonable life expectancy. However, patient groups were balanced for MDS subtypes, IPSS, and anti-MDS treatment. The cohort of chelated patients had a lower mean hemoglobin level and a higher transfusion need, disease characteristics that are known risk factors for reduced survival in MDS [1,6,7]. One might preferentially select these patients as an important target population for ICT.

Despite these concerns and recognizing that causality cannot be inferred from our study, the observation of a more than threefold higher median survival of patients treated with ICT in this particular cohort of patients makes the value of ICT even more compelling. Our study therefore adds additional evidence to the already published studies showing that adequate chelation of transfusion-dependent Low/Int-1 patients does more than just reducing serum ferritin levels, but is associated with longer survival of patients. However, as observational effectiveness studies do not provide causal evidence, randomized trials of ICT remain a necessity. In that regard the results of the ongoing TELESTO trial (NCT00940602) are awaited as prospective evidence that ICT reduces mortality in transfusion-dependent Low/Int-1 patients.

Mortality among patients chelated for 6 months or more was 32% compared to 70% among non-chelated patients. However, this difference in mortality was not related to MDS disease progression. In contrast, the crude cardiac mortality rate was 4 times higher in the non-chelated cohort.

As with ABE02, ABE03 was a retrospective observational study in one European country, not a prospective population-based cohort study with random subject selection. The study did not examine the comparative effectiveness of ICT regimens and serum ferritin was the only marker of iron status. Future studies may benefit from more sensitive markers like nontransferrin-bound iron or labile plasma iron, but these are as of yet not generally established markers.

In summary, we have confirmed that adequate ICT, preferably for six months or longer, is associated with markedly prolonged overall survival in transfusion-dependent patients with lower risk MDS. This suggests that, in the Low/Int-1 risk subpopulation of MDS patients, ICT may have a patient survival benefit. Patient convenience and comfort associated with deferasirox therapy must be considered in clinical decision-making.

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Conflict of interest

WP is employed by Novartis Pharma. IA, AH, and KM are employees of Matrix45. By company policy, they are prohibited from owning equity in client organizations (except through mutual funds or other independent collective investment instruments) or contracting independently with client organizations. Matrix45 provides similar services to other biopharmaceutical companies on a non-exclusivity basis. MD, DS, YB, LN, WW, KT, DD, CR, AF, CG and FT have served on advisory boards for Novartis Pharma. All other authors declare no competing financial interests.

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